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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/100443 A2

(54) Title: METHOD AND APPARATUS FOR IDENTIFYING TISSUE WITHIN THE BODY USING A FLUORESCENT DYE

(57) Abstract: A method and apparatus are disclosed for localizing or identifying specific tissue within the body, such as lymphatic tissue, using a fluorescent dye. A fluorescent dye such as fluorescein sodium or indocyanine green ("ICG") dye is injected into the body adjacent a diseased tissue site, e.g., a cancer site. Preferably, the dye is injected at multiple locations about the periphery of a cancerous lesion. Alternatively, the dye can be injected into the body at any site that will deliver the fluorescent dye to the lymphatic basin associated with the lesion. After injection, the fluorescent dye will enter the lymphatic system associated with the area of cancer. The lymphatic system can be visually identified using a fluorescence detector. The fluorescence detector preferably includes a light source having the particular wavelength of light necessary to create excitation of the fluorescent dye. The fluorescence detector may also include a viewing filter for allowing direct visualization of the fluorescent light emission, while blocking the light emitted by the light source. A fiber-optic light guide may be provided to carry light from the light source to the area of interest. In one preferred method, the sentinel node (the first node in a lymphatic node cluster) is identified using a fluorescent dye by visually tracing the lymphatic system from the injection site to the regional lymph nodes.

METHOD AND APPARATUS FOR IDENTIFYING TISSUE WITHIN THE BODY USING A FLUORESCENT DYE

BACKGROUND

1. Technical Field

The present disclosure relates generally to a method and apparatus for identifying specific tissue within the body by injection of a fluorescent dye into a fluid flow stream within the body upstream of the specific tissue. More specifically, the present disclosure relates to a method for identifying the sentinel node of a lymph node cluster using a fluorescent dye injected into the lymph system upstream of the lymph nodes and to an apparatus for viewing or localizing the fluorescent dye within the body.

2. Background Of Related Art

The lymphatic system is the body's network of organs, ducts, and tissues that filter harmful substances out of the fluid that surrounds body tissues. Lymph nodes are the lymphatic system's battle stations against infection. It is in the nodes where blood cells engulf and destroy debris to prevent the debris from reentering the bloodstream. Lymph nodes are connected to one another by lymphatic vessels. Clusters of lymph nodes are found in the pelvic region, underarm, neck, chest and abdomen. Although lymph nodes commonly enlarge to fight infection and disease, such as cancer, an overwhelming infection can leave a lymph node and travel through the lymphatic system to other nodes and to other body tissues. Cancer can spread very easily through the lymph system.

The use of lymphatic mapping as an important cancer staging technique is well known. The surgical identification of lymph nodes which receive lymphatic drainage from a tumor site provides prognostic information as to the extent of the disease. The use of radioactive materials to tag tissue within a patient for effecting its localization and demarcation by radiation detecting devices has been disclosed in medical literature for many years. In fact, the use of radioactive materials is

becoming an established modality in the diagnosis and/or treatment of diseases such as cancer.

The use of radioactive materials to identify specific tissue within the body has several drawbacks associated therewith. Firstly, there are long term health risks associated with injecting a radioactive material into a patient's body. Secondly, the instrumentation required to view the radioactive material within the body is sophisticated and expensive. Finally, a surgeon must wait four or more hours after injection of a radioactive material into the body before diseased tissue can be identified and a surgical procedure such as a biopsy can be conducted.

U.S. Patent Nos. 6,304,771 ("'771 patent") and 5,917,190 ("'190 patent") disclose object imaging devices using diffuse light. The '771 patent discloses imaging of a fluorescent object such that diffuse photon density waves having a first wavelength cause the object to fluoresce to produce re-radiated diffuse photon density waves having a second wavelength. A detector is able to detect the re-radiated diffuse photon density waves such that a processor can image the object. The '771 and '190 patents are incorporated herein by reference in their entirety.

Accordingly, a continuing need exists for a method and apparatus for identifying specific tissue within the body which is not harmful to a patient, inexpensive, and can be performed within a reasonable proximity of a surgical procedure such as a biopsy.

SUMMARY

In accordance with the present disclosure, a method and apparatus are disclosed for localizing or identifying specific tissue within the body, such as lymphatic tissue, using a fluorescent dye. A fluorescent dye such as fluorescein sodium or indocyanine green ("ICG") dye is injected into the body adjacent a diseased tissue site, e.g., a cancer site. Preferably, the dye is injected at multiple locations about the periphery of a cancerous lesion. Alternately, the dye can be injected into the body at any site that will deliver the fluorescent dye to the lymphatic basin associated with the lesion. The appropriate dosage of dye material will depend on the particular dye being used and on the particular procedure being performed.

After injection, the fluorescent dye will enter the lymphatic system associated with the area of cancer. Approximately twenty minutes after the dye has been

injected into the body, the lymphatic system can be visually identified using a fluorescence detector. The fluorescence detector preferably includes a light source having the particular wavelength of light necessary to create excitation of the fluorescent dye. The fluorescence detector may also include a viewing filter for allowing direct visualization of the fluorescent light emission, while blocking the light emitted by the light source. A fiber-optic light guide may be provided to carry light from the light source to the area of interest.

In one preferred method, the sentinel node (the first node in a lymphatic node cluster) is identified using a fluorescent dye by visually tracing the lymphatic system from the injection site to the regional lymph nodes. The lymphatic system can be viewed directly or viewed transdermally. Once the sentinel node has been identified, the node may be surgically excised for pathologic evaluation, or evaluated in-situ for metastatic disease.

BRIEF DESCRIPTION OF THE DRAWINGS

Preferred embodiments of the presently disclosed method and apparatus for identifying tissue within the body using a fluorescent dye are described herein with reference to the drawings wherein:

FIG. 1 is a schematic view of one preferred embodiment of the presently disclosed fluorescence detector;

FIG. 2 is a schematic view of the presently disclosed fluorescence detector including a viewing filter; and

FIG. 3 is a schematic representation of a portion of a body illustrating a fluorescent dye being injected into the body and illustrating regional lymph nodes and lymphatic channels.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Preferred embodiments of the presently disclosed method and apparatus for identifying tissue within the body will now be described in detail with reference to the drawings, wherein like reference numerals designate corresponding elements in each of the several views.

FIGS. 1 and 2 illustrate a schematic representation of a fluorescence detector shown generally as 10. Fluorescence detector 10 includes a light source 12 for

generating light having a particular wavelength necessary to create excitation of a fluorescent dye, a fiber-optic light guide 14 for directing the light generated by light source 12 to a distant location, and an optical filter 16. Fiber-optic light guide 14 can be constructed from a sterile disposable material such as [?]. Alternately, light guide 14 can be formed of a reusable material which is covered by a sterile drape (not shown). Light source 12 preferably includes a power cord 18 for engaging an electrical outlet (not shown). Alternately, other power sources, e.g., batteries, may be used to supply power to light source 12. Preferably, light source 12 includes a tungsten-halogen lamp 20, although the use of other lamp types is also envisioned. Referring to FIG. 2, fluorescence detector 10 may also include a viewing filter 22. Viewing filter 22 allows for direct visualization of fluorescent light emissions from a fluorescent dye produced by application of light generated by light source 12 to the fluorescent dye.

The above-identified fluorescence detector 10 can be used in the method and apparatus for identifying specific tissue within the body to be discussed below. Alternately, other fluorescence detector apparatus or systems may be used to detect and view fluorescent emissions from a fluorescent dye.

The present disclosure is directed to a method for identifying and viewing specific tissue within the body using a fluorescent dye. The method, to be discussed in detail below, is particularly suitable for identifying the sentinel node of a lymph node cluster of the lymphatic system.

Referring to FIGS. 2 and 3, the presently disclosed method for identifying specific tissue within the body, such as the sentinel node of a lymph node cluster of the lymphatic system, includes injecting a fluorescent dye into the body adjacent a diseased tissue site, e.g., cancerous lesion, using, for example a syringe 21 or other known injection device. Fluorescent dyes which can be used to perform the method include fluorescein sodium and indocyanine green. The use of other fluorescent dyes approved by the FDA for internal use is also envisioned. Preferably, the fluorescent dye is injected in multiple locations 26 (FIG. 3) about the periphery of diseased tissue 30 without injecting the dye into the diseased tissue. Generally, the injections will be positioned within one centimeter of the diseased tissue. Alternately, the fluorescent dye can be injected into the body at any site that will deliver the fluorescent dye to the lymphatic basin associated with the diseased tissue. For example, in identifying the

sentinel node in the breast region, fluorescent dye injected around the areolar will be as effective as fluorescent dye injected adjacent the tumor site. The appropriate dosage or quantity of fluorescent dye injected into the body will vary from procedure to procedure and based upon the particular fluorescent dye being used.

After the fluorescent dye has been injected into the body at an appropriate location, it will typically take about twenty minutes for the dye to flow through the lymphatic system into the regional lymph node cluster associated with the area of diseased tissue. Accordingly, about twenty minutes after injection of the fluorescent dye, a fluorescence detector can be used in the manner discussed above to identify specific tissue within the body, e.g., tissue to be biopsied such as the sentinel node of a lymph node cluster.

In use, fluorescence detector 10 is positioned to direct light having a particular wavelength necessary to create excitation of the fluorescent dye onto the body tissue such that the body tissue, e.g., the lymphatic system, can be optically or non-optically viewed. The light may be directed transdermally to allow transdermal viewing of the diseased tissue, e.g., sentinel node, or the light may be applied directly to internal tissue during an open surgical procedure. Alternately, the light may be directed onto the diseased tissue during an endoscopic procedure. An endoscopic procedure may require insufflation of the area adjacent tissue.

During a procedure to identify a sentinel node of a lymph node cluster, the lymphatic system including lymphatic channels 40 and regional lymph nodes 42, can be identified and viewed using the fluorescence detector to determine the sentinel node or the sentinel node of a lymph node cluster. Thereafter, only the first node can be excised for pathologic evaluation or evaluated in-situ for metastic disease. The entire lymph node cluster need not be excised.

It will be understood that various modifications may be made to the embodiments disclosed herein. For example, the materials used to construct the individual components of the device may be chosen from a variety of known materials to achieve the desired result. Therefore, the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. Those skilled in the art will envision other modifications within the scope and spirit of the claims appended hereto.

WHAT IS CLAIMED:

1. A method for identifying specific tissue in a body without using a radioactive signature comprising the following steps:

injecting a fluorescent dye into the body at a location to deliver the dye to a lymphatic basin;

providing a fluorescence detector having a light source for generating light having a wavelength to create excitation of the fluorescent dye;

directing the light source at the body; and

viewing and identifying specific tissue in the body based on a flow of fluorescent dye.

2. A method according to Claim 1, wherein the specific tissue is a sentinel node of a lymph node cluster.

3. A method according to Claim 2, wherein the step of injecting a fluorescent dye includes injecting a fluorescent dye at multiple locations about a cancerous lesion.

4. A method according to Claim 1, wherein the step of providing a fluorescence detector includes providing a fiber optic light guide.

5. A method according to Claim 4, wherein the step of providing a fluorescence detector includes providing a viewing filter.

6. A method according to Claim 2, wherein the fluorescent dye includes indocyanine green.

7. A method according to Claim 2, wherein the fluorescein sodium.

8. A method according to Claim 1, further including the following step: excising the specific tissue subsequent to identifying the specific tissue.

9. A method according to Claim 1, wherein the step of viewing and identifying the specific tissue in the body includes viewing the specific tissue transdermally.

10. A method according to Claim 1, wherein the step of viewing and identifying the specific tissue in the body includes directly viewing the specific tissue.

11. A method according to Claim 4, wherein the fiber optic light guide is disposable.

12. A method according to Claim 1, wherein the step of viewing includes optically visualizing specific tissue in the body.

13. A fluorescence detector comprising:

a light source for generating light having a wavelength to create excitation of a fluorescent dye; and

a fiber optic light guide for directing the light generated by the light source towards body tissue.

14. A fluorescent detector according to Claim 13, further including a viewing filter for allowing direct visualization of a fluorescent light emission from the fluorescent dye and blocking the light generated by the light source.

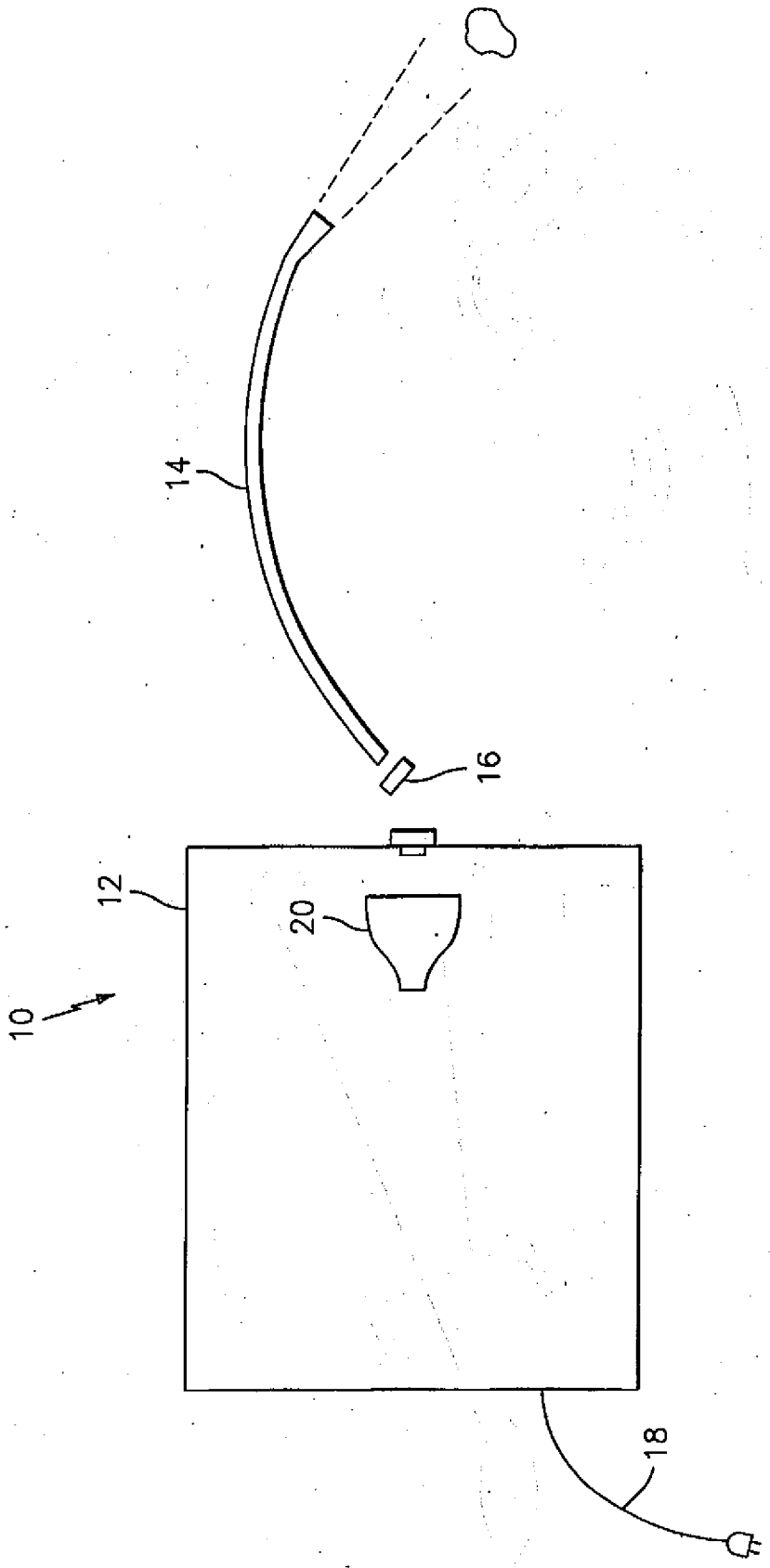

FIG. 1

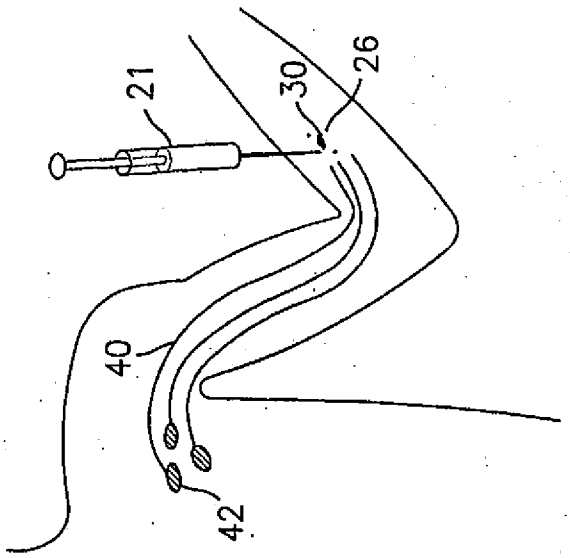

FIG. 3

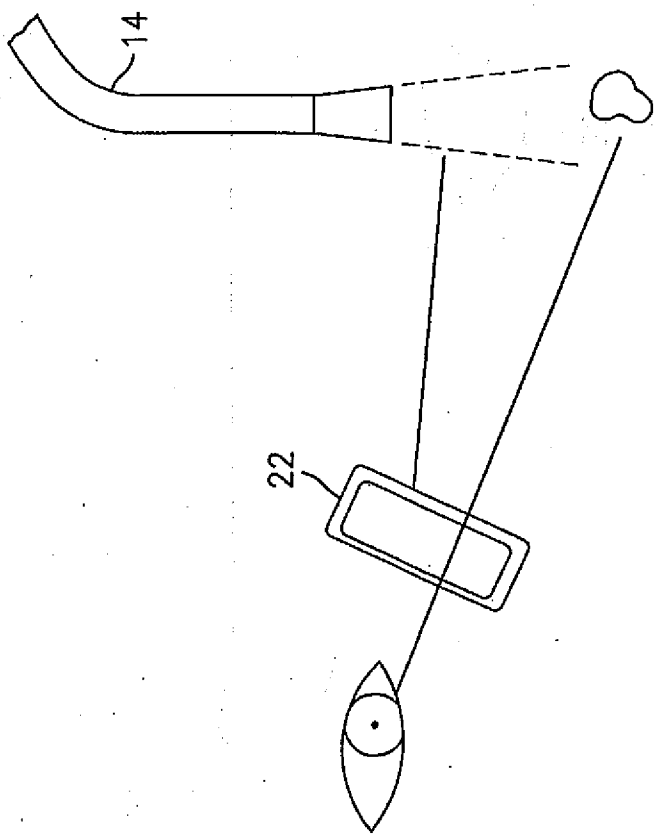

FIG. 2

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(71) Applicant *(for all designated States except US)*: **TYCO HEALTHCARE GROUP LP** [US/US]; 150 Glover Avenue, Norwalk, CT 06856 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **DEPIERRO, Scott** [US/US]; 69 Bishop Lane, Madison, CT 06443 (US).

(74) Agent: **DENNINGER, Douglas, E.**; Tyco Healthcare Group LP, 150 Glover Avenue, Norwalk, CT 06856 (US).

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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
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(88) Date of publication of the international search report:
20 November 2003

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(54) Title: IDENTIFYING TISSUE WITHIN THE BODY USING A FLUORESCENT DYE

(57) Abstract: A method and apparatus are disclosed for localizing or identifying specific tissue within the body, such as lymphatic tissue, using a fluorescent dye. A fluorescent dye such as fluorescein sodium or indocyanine green ("ICG") dye is injected into the body adjacent a diseased tissue site, e.g., a cancer site. Preferably, the dye is injected at multiple locations about the periphery of a cancerous lesion. Alternatively, the dye can be injected into the body at any site that will deliver the fluorescent dye to the lymphatic basin associated with the lesion. After injection, the fluorescent dye will enter the lymphatic system associated with the area of cancer. The lymphatic system can be visually identified using a fluorescence detector. The fluorescence detector preferably includes a light source having the particular wavelength of light necessary to create excitation of the fluorescent dye. The fluorescence detector may also include a viewing filter for allowing direct visualization of the fluorescent light emission, while blocking the light emitted by the light source. A fiber-optic light guide may be provided to carry light from the light source to the area of interest. In one preferred method, the sentinel node (the first node in a lymphatic node cluster) is identified using a fluorescent dye by visually tracing the lymphatic system from the injection site to the regional lymph nodes.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/18627

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K49/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KERSEY T W ET AL: "Comparison of intradermal and subcutaneous injections in lymphatic mapping" JOURNAL OF SURGICAL RESEARCH 2001 UNITED STATES, vol. 96, no. 2, 2001, pages 255-259, XP002244921 ISSN: 0022-4804 abstract; figure 1 -----	1-14
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 June 2003	02/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Berte, M.

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& JAPANESE JOURNAL OF GASTROENTEROLOGICAL SURGERY 2001 JAPAN, vol. 34, no. 5, 2001, page 520, ISSN: 0386-9768	
X	HAWRYSZ D J ET AL: "Developments toward diagnostic breast cancer imaging using neer-infrared optical measurements and fluorescent contrast agents" NEOPLASIA 2000 UNITED STATES, vol. 2, no. 5, 2000, pages 388-417, XP0008012159 ISSN: 1522-8002 abstract	1-14
X	LEVENBACK C ET AL: "Intraoperative lymphatic mapping for vulvar cancer" OBSTETRICS AND GYNECOLOGY 1994 UNITED STATES, vol. 84, no. 2, 1994, pages 163-167, XP0008018263 ISSN: 0029-7844 abstract; figure 1	1-14
X	MOESTA K T ET AL: "Fluorescence as a concept in colorectal lymph node diagnosis." RECENT RESULTS IN CANCER RESEARCH. FORTSCHRITTE DER KREBSFORSCHUNG. PROGRES DANS LES RECHERCHES SUR LE CANCER. 2000, vol. 157, 2000, pages 293-304, XP0008018266 ISSN: 0080-0015 abstract page 298, paragraph 2	1-14
X	WO 00 21576 A (LUIKEN GEORGE A ; FLUORO PROBE INC (US)) 20 April 2000 (2000-04-20) page 10, line 24 - page 11, line 7; claims 1,6,8,9,19,26,28	1-14
P,X	ICHIKURA TAKASHI ET AL: "Sentinel node concept in gastric carcinoma." WORLD JOURNAL OF SURGERY. MAR 2002, vol. 26, no. 3, 31 March 2002 (2002-03-31), pages 318-322, XP002244922 ISSN: 0364-2313 abstract; table 3	1-14
E	WO 02 088666 A ((SALO, J.; LOMA LINDAUNIVERSITY SURGERY MEDICAL GROUP INC (US)) 7 November 2002 (2002-11-07) claims 1,4,5,9,11,14,17,18,22	1-14

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 02 074171 A (UNIVERSITY OF UTAH RESEARCH FOUNDATION) 26 September 2002 (2002-09-26) claims 1,3,6,12	1-14

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/US 02/18627

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-12 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/18627

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